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ORIGINAL RESEARCH ARTICLE

Dabigatran Does Not Prolong the QT Interval with Supratherapeutic Exposure: a Thorough QT Study in Healthy Subjects

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Abstract

Background Dabigatran etexilate is a pro-drug of the oral reversible direct thrombin inhibitor dabigatran that interacts with the active site in the catalytic domain of the thrombin molecule.

Objective To assess the electrophysiological effects of therapeutic and supratherapeutic doses of dabigatran etexilate in healthy subjects, a thorough QT study was performed.

Methods In this single-centre, blinded, placebo- and active-controlled, four-period, crossover study, 40 healthy Caucasian subjects (20 women and 20 men) received single oral doses of dabigatran etexilate (150 mg and 600 mg), moxifloxacin 400 mg (positive control) or placebo, in a randomized order. Electrocardiogram (ECG) profiles were recorded at baseline and during the randomized study treatment in each period. The individually heart-rate–corrected QT interval (QTcI) was the primary parameter. The primary endpoint was the mean of these QTcI values obtained at 1.5, 2 and 3 h following study drug administration minus the mean of the time-matched QTcI values obtained at baseline day −1. The hypothesis tested was that the difference between each of the two doses of dabigatran etexilate (150 mg and 600 mg) and placebo, for the mean time-matched change from baseline (CfB) of QTcI between 1.5 and 3 h (the primary endpoint), was greater than or equal to 10 ms. Secondary endpoints were the time-matched CfB of QTcI between 0.5 and 24 h post-dose.

Results All subjects completed the study without premature discontinuation and all treatments were well tolerated. Following dabigatran etexilate administration, the mean values of the placebo-adjusted time-matched CfB of QTcI between 1.5 and 3 h post-dose were close to 0; the upper bound of the two-sided 90 % confidence interval (CI) was 1.4 ms for dabigatran etexilate 150 mg and 1.3 ms for dabigatran etexilate 600 mg. The placebo-adjusted time-matched CfB of QTcI remained close to 0 at all time points, and all 90 % CIs were between −5 ms and 5 ms, well below the pre-defined non-inferiority margin of 10 ms.

Conclusion This thorough QT study demonstrated that therapeutic and fourfold supratherapeutic doses of dabigatran etexilate do not prolong QT intervals.

The study was presented at the 60th Annual Scientific Session of the American College of Cardiology and the abstract has been published (J Am Coll Cardiol 2011;57: 56).

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1 Introduction

Vitamin K antagonists (VKAs), such as warfarin, and injectable anticoagulants, including heparins, have been the cornerstone of anticoagulant therapy for decades. However, VKAs have a narrow therapeutic window, numerous drug and food interactions, and require routine monitoring and

dose adjustments [1]. Heparins require parenteral administration, which can be difficult when chronic use is required [2, 3].

Dabigatran etexilate is an oral pro-drug, which is rapidly converted to dabigatran, a direct thrombin inhibitor [4]. Dabigatran has predictable pharmacokinetic (PK) and pharmacodynamic properties, is predominantly excreted renally and has a half-life of 12–17 h [4, 5]. It does not require anticoagulation monitoring or multiple dose adjustments [6]. Dabigatran etexilate has a similar safety and efficacy profile to enoxaparin sodium for the prevention of venous thromboembolism (VTE) after knee or hip replacement [7–11]. Furthermore, dabigatran etexilate 150 mg twice daily shows superiority to warfarin in moderate to high risk patients with non-valvular atrial fibrillation (AF) in reducing the risk of stroke (ischaemic and haemorrhagic) and systemic embolism and intracranial haemorrhage, without an increase in major bleeding [7, 12–15].

Drugs may induce QT prolongation, which can result in adverse cardiac events [16]. The QT interval indirectly represents ventricular depolarization and subsequent repolarization; prolonged QT intervals can increase the risk of cardiac pro-arrhythmias such as *torsade de pointes*, which may result in sudden death [16].

To our knowledge, there are no previously published evaluations of the effect of dabigatran on cardiac repolarization that are considered compliant with regulatory standards [International Conference on Harmonisation (ICH) E14 Guidance] [17]. In pre-clinical studies, supratherapeutic dabigatran [up to 3 mg/kg intravenously; nearly 100 times the median effective dose (ED_{50})] had no influence on cardiovascular parameters [18]. In isolated guinea pig papillary muscles, no noteworthy changes in QT interval were observed with dabigatran stimulation [concentrations up to 10 μmol/L, approximately 2,000-fold the inhibition constant (K_i) for thrombin], indicating a lack of effect on cardiac ion channels [19]. As blockade of the human *Ether-à-go-go*-Related Gene (hERG)-mediated potassium current is the most common mechanism of drug-induced prolongation of the myocardial action potential and QT-interval prolongation, data showing that dabigatran did not modify the hERG-mediated potassium current in human embryonic kidney cells agree with the previously mentioned pre-clinical results [20]. Taken together, these results suggest that dabigatran does not prolong QT intervals in pre-clinical evaluations.

Studies to evaluate the effects of drugs on cardiac repolarization and the QT interval are designed to detect modest changes on the ECG. Consequently, they are generally randomized, conducted in healthy subjects, and include a placebo and an active positive-control group. The current study was performed specifically to assess the electrophysiological effects of clinical and supratherapeutic doses of dabigatran etexilate (150 mg and 600 mg, respectively) compared with placebo and the active control moxifloxacin in healthy subjects. It was conducted in 2006 as part of the clinical development of dabigatran etexilate and was previously published as an abstract and presented as a poster at the American College of Cardiology Scientific Sessions in 2011.

2 Materials and Methods

2.1 Study Design and Randomized Treatments

This was a randomized, placebo-controlled, four-treatment, four-period crossover study. Dabigatran etexilate 150 mg or 600 mg, or placebo, was administered in a double-blind, double-dummy manner (as four capsules, using a combination of placebo and/or dabigatran etexilate 150-mg capsules as appropriate). The positive control (400 mg moxifloxacin, Avelox®; Bayer Vital, Leverkusen, Germany) was given as one open-label capsule.

Study medication was administered with 240 mL of water following an overnight fast of at least 10 h. A washout of at least 5 days between subsequent visits was required (Fig. 1a). All participants were kept under medical surveillance for 24 h post-dose. Breakfast, a light lunch and dinner were provided 1.5, 4 and 10 h post-dose, respectively, and an optional light snack was offered 7 h post-dose (all after ECG recordings and PK samples were taken).

The four treatments were included in 12 sequences based on three orthogonal Williams's squares, as recommended for thorough QT studies because it is variance balanced and adjusts for potential carryover effects [21, 22]. This design ensures double-blind conditions for placebo and dabigatran etexilate treatments, while allowing for open-label administration of moxifloxacin.

The active control was included to demonstrate that the study had adequate sensitivity to detect a small, but significant, drug-induced QT-prolonging effect. Moxifloxacin produces a modest QT-interval prolongation (8–14 ms) after a single dose [23] and is the most commonly used positive control [24, 25]. Its peak plasma concentration occurs 1–4 h following an oral dose without food and its PK half-life is about 12 h.

The clinical trial protocol and other relevant study documents were reviewed and approved on 21 February 2006 by the responsible ethics committee: Ethikkommission der Landesärztekammer Baden-Württemberg, Jahnstraße 40, D-70597 Stuttgart, Germany. This trial was performed in accordance with the protocol, the principles laid down in the Declaration of Helsinki (1996), the ICH Harmonised Tripartite Guideline for Good Clinical Practice (GCP) and applicable regulatory requirements. In the

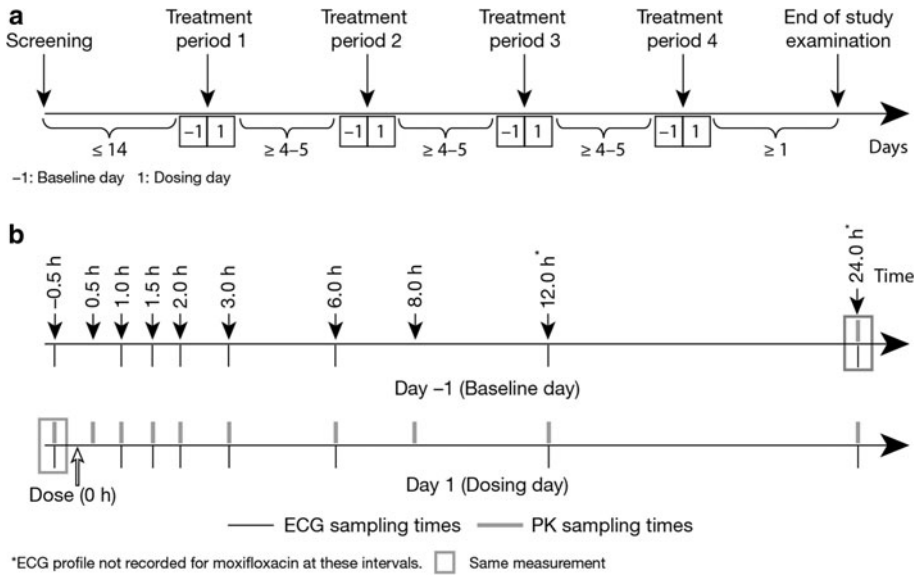

Fig. 1 Elements of the study design: (**a**) schedule of the visits; (**b**) timing of the ECG and pharmacokinetic measurements. 'Same measurement' refers to the ECG recording at 'day 1, 0.5 h' being used as a time-matched data point for both 'day −1, −0.5 h' and 'day 1, 24.0 h. *ECG* electrocardiogram, *PK* pharmacokinetic

European Clinical Trials Database, this study is included as EudraCT 2005-006154-13.

2.2 Subjects

A total of 40 healthy female and male Caucasian subjects were recruited from the volunteer pool of the Human Pharmacology Centre, Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany; each sex was to represent at least one-third of the study population. All participants provided written informed consent in compliance with GCP and local laws and regulations. Subjects aged 18–65 years with a body mass index (BMI) of 20.0–29.9 kg/m^2 were screened and selected according to a complete medical history, including physical examination, vital signs, 12-lead ECG and clinical laboratory tests.

Subjects were excluded if they exhibited ECG values outside the reference range for clinical relevance: heart rate (HR) <45 beats/min (bpm) or >80 bpm; PR interval >220 ms; QRS interval >120 ms; QT interval >470 ms; or corrected (c) QT intervals, namely QTcF (Fridericia) or QTcB (Bazett) >450 ms; or if they had any history of pathological bleeding.

2.3 ECG Assessment

ECG profiles were obtained at baseline (day −1) and on the day of treatment (day 1), at the same clock time (time matched) within each of the four treatment periods (Fig. 1a). ECGs were taken after subjects had rested for at least 10 min in the supine position. ECGs were recorded in triplicate, 30–120 sec apart, to account for inherent variability; each recording lasted 10 sec. They were performed at pre-defined times [−0.5 (baseline), 1, 1.5, 2, 3, 6, 12 and 24 h; the last two time points were omitted for moxifloxacin (Fig. 1b)]. The time point −0.5 was used as the time-matched baseline for the 24-h time point. ECGs were recorded digitally, in compliance with regulatory guidance for annotated digital ECGs [17], using a Corina CardioSoft electrocardiograph (ECG) and MUSE CV cardiology system (General Electric Medical Systems, Freiburg, Germany). ECG readings were sent electronically to a central laboratory for semi-automated interval measurement (using manual over-read of automatically determined fiducial interval marks) of R wave to R wave (RR), PR, QRS and QT intervals.

For each ECG, the ECG intervals were determined from four wave forms, preferably in lead II. Hence, the triplicate ECG recordings resulted in data from 12 wave forms. The average of these values formed the ECG interval endpoints for each of the time points. The laboratory performing the ECG interval measurements and assessments was blinded with regard to all treatments used, including moxifloxacin, and to timing of the ECGs.

2.4 Pharmacokinetic Evaluation

Subjects were cannulated and blood samples for dabigatran PK measurements were collected at the same time points as the ECG recordings (predose, 1, 1.5, 2, 3, 6, 12 and 24 h), to investigate potential exposure-response relationships and confirm the availability of the drug.

Plasma concentrations of free, non-conjugated dabigatran, of total (free and conjugated) dabigatran (after alkaline cleavage of conjugates) and of the pro-drug (dabigatran etexilate) and its intermediates (BIBR1087 and BIBR 951) were analysed using a validated high-performance liquid chromatography tandem mass spectrometry method at

NUVISAN GmbH, Neu-Ulm, Germany, as previously reported [5]. No PK measurements were taken during moxifloxacin treatment, as the active control is used to demonstrate assay sensitivity for the primary analysis only.

2.5 Safety Profile Evaluation

Safety was assessed by recording adverse event withdrawals, the incidence and intensity of adverse events, laboratory assessments, vital signs and weight. During screening and the end of study evaluation, vital signs were recorded after the subject had been supine for at least 10 min. At screening, pre-dose and end-of-study, clinical laboratory parameters were assessed after fasting for at least 10 h. Tolerability was investigator-assessed using adverse event reports and laboratory evaluations, and was categorized as 'good', 'satisfactory', 'not satisfactory' or 'bad'.

2.6 Study Endpoints and Statistical Considerations

2.6.1 Primary and Secondary Endpoints

As the primary parameter, the individual heart-rate–corrected QT interval (QTcI) was chosen. The primary endpoint was derived as the average of the QTcI values obtained 1.5, 2 and 3 h post-dose minus the average of the time-matched QTcI values obtained at baseline (day −1) in each study period. Plasma levels of dabigatran and moxifloxacin were expected to be at least 75 % of their peak during this period, which thus represented the highest expected exposure.

The null hypothesis was that the difference between each of the two doses of dabigatran etexilate (150 mg and 600 mg) and placebo for mean change from baseline (CfB) for the QTcI was greater than or equal to 10 ms, according to regulatory guidance [17]. This test was performed one-sided at the 5 % significance level, which is equivalent to the upper limit of the two-sided 90 % confidence intervals (CIs). To conclude that dabigatran etexilate was non-inferior to placebo, the null hypothesis had to be rejected for both doses simultaneously; hence no adjustment for multiple testing was necessary.

Secondary endpoints included: (i) the mean of the CfB for QTcI from all ECGs taken from 1 to 6 h post-dose and (ii) the time-matched CfB for QTcI at any time point between 0.5 and 24 h post-dose.

Other parameters of interest included the other QT correction formulas (study population, QTcN; Fridericia, QTcF; Bazett, QTcB, see below). In addition, the uncorrected QT interval and heart rate were analysed. All inferential analyses were performed separately for all of these parameters, while the primary emphasis was the evaluation of the QTcI endpoints.

Notable changes post-baseline in QTcI, QTcN, QTcF, QTcB or the uncorrected QT interval were assessed using the thresholds in compliance with regulatory guidance [17]: the new onset of QTc greater than 450, 480 or 500 ms post-baseline, time-matched CfB of QTc of greater than 30 or 60 ms, and new onset of QT interval greater than 500 ms.

2.6.2 Heart Rate Correction Models

Changes in heart rate can influence QT interval length. Furthermore, heart rate correction should be performed to improve the accuracy for detecting drug-induced QT prolongation and to overcome potential effects of diurnal variation [26]. We used an individual heart rate correction derived from all baseline log-transformed QT and RR interval data for each subject.

The general formula is:

$$\mathrm{QTc[ms]} = (1000/\mathrm{RR[ms]})^{\mathrm{slope}} \cdot \mathrm{QT[ms]}$$

The slope was determined using a multi-level model including subject and period as factors that accounted for potential differences between the baseline periods [27]. For the individual correction QTcI, the slopes were determined individually, while for the population correction QTcN, one study population slope was derived. QTcF ($QT/RR^{1/3}$) and QTcB ($QT/RR^{1/2}$) were also determined.

2.6.3 Statistical Models

The primary endpoint (average of the time-matched CfB of the QTcI between 1.5 and 3 h post-dose) for placebo and both doses of dabigatran etexilate was evaluated using an analysis of covariance (ANCOVA) model for crossover data. The model accounted for the following sources of variation: 'sequence', 'period' and 'treatment' as fixed effects, 'subjects nested within sequences' as a random effect and 'baseline' as a covariate.

Analysis of secondary endpoints, time-matched CfB of the QTcI at any time between 1 and 24 h post-dose, used the Patterson repeated measurements model [28], which accounts for 'time' as a repeated effect with an unstructured covariance matrix. All observed data were used.

All analyses were also performed similarly with regard to moxifloxacin-induced changes in QTcI [22]. Finally, an exposure-response analysis of the placebo-corrected time-matched CfB of QTcI for dabigatran (with subject as a factor and dabigatran concentration as a linear covariate) was performed as a post hoc analysis, as proposed by Garnett et al [29].

2.6.4 Sample Size

The sample size was determined using published recommendations for a thorough QT study [30] and using an expected variability of the primary endpoint of 9.5 ms

[31, 32]. Based on the absence of QT effects in pre-clinical *in vivo* and *in vitro* studies and human clinical trials, a minimal expected difference of 1 ms between dabigatran and placebo was selected, leading to a sample size of 36 subjects to demonstrate non-inferiority with a power of 90 %. This sample size was also sufficient to detect a difference of 9 ms in the mean time-matched CfB of QTcI between moxifloxacin and placebo with a power of 90 %. To account for potential dropouts and/or unevaluable data points, 40 subjects were included in the trial.

3 Results

3.1 Subject Demographics and Disposition

Forty subjects were enrolled, randomized and received study medication between 23 March until 26 May 2006; all 40 completed the trial (Table 1).

3.2 Individual Heart-Rate–Corrected QTcl

3.2.1 Primary Endpoint

The primary endpoint, mean time-matched CfB of QTcI between 1.5 and 3 h post-dose, was −4.6 ms for placebo, −4.9 ms for dabigatran etexilate 150 mg and −5.0 ms for dabigatran etexilate 600 mg (Table 2). The mean estimate of the placebo-adjusted CfB was close to 0 ms; the upper bound of the two-sided 90 % CI was 1.4 ms for dabigatran etexilate 150 mg and 1.3 ms for dabigatran etexilate 600 mg (Fig. 2; Table 2). Hence the null hypothesis was rejected, and this thorough QT trial demonstrated that dabigatran etexilate does not have a meaningful impact on the QT interval.

Table 1 Summary of subject disposition, demographic characteristics and ECG measures

Demographic	Total
Randomized and treated subjects, n (%)	40 (100)
Completed, n (%)	40 (100)
Sex, n (%)	
Male	20 (50)
Female	20 (50)
Age (y)	38.6 (7.7)
Height (cm)	173.4 (7.9)
Weight (kg)	73.0 (10.9)
BMI (kg/m^2)	24.2 (2.5)
Heart rate (bpm)	62.3 (8.0)
QT interval (ms)	398.4 (28.9)
QTcI (ms)	401.1 (23.3)

Data are given as mean (standard deviation) except where indicated otherwise

BMI body mass index, *bpm* beats per minute, *ECG* electrocardiogram, *QTcl* heart-rate–corrected QT interval

3.2.2 Secondary Endpoints

The mean time-matched CfB of QTcI between 1 and 6 h post-dose was −5.2 ms for placebo, −5.3 ms for dabigatran etexilate 150 mg and −5.4 ms for dabigatran etexilate 600 mg. The mean estimate of the placebo-adjusted CfB of QTcI was close to 0 ms and the upper bound of the two-sided 90 % CI was 1.5 ms for dabigatran etexilate 150 mg and 1.4 ms for dabigatran etexilate 600 mg (Fig. 2).

The largest time-matched CfB of the QTcI between 0.5 and 24 h post-dose was slightly negative at all times for both dabigatran etexilate doses. The upper bound of the two-sided 90 % CI of the largest time-matched mean difference from placebo was approximately 3 to 4 ms at both dose levels, and all 90 % CIs were between –5 ms and 5 ms (Table 3). Therefore, non-inferiority was also achieved in the secondary analyses for both doses of dabigatran etexilate.

3.2.3 Exposure-Response Analysis

The exposure-response analysis was introduced post hoc to compare the results with those of the primary analysis. The slope between total and free dabigatran concentration and the placebo-corrected time-matched CfB of QTcI was close to 0, and the 90 % CI of the predicted value of this parameter at the geometric mean (gMean) maximum plasma concentration (C_{max}) associated with each dose was below 3 ms for all four analyses (Table 4). Hence, the results of the exposure-response analysis were in full agreement with the primary and secondary endpoint analyses.

3.2.4 Assay Sensitivity

For the positive control moxifloxacin, the mean time-matched CfB of QTcI between 1.5 and 3 h post-dose was 9.4 ms (Table 2), leading to a placebo-adjusted CfB of 14.2 ms (90 % CI 12.3–16.2) (Fig. 2; Table 2), which was above the margin of 5 ms defined in regulatory guidance. The largest time-matched CfB observed 0.5–24 h post-dose was reported at 2 h and produced a placebo-adjusted difference of 14.1 ms (90 % CI 11.4–16.7; Table 3). The time profile of QTcI was as expected, the profile has a clear peak (at the time of the expected maximum exposure) and a sufficient declining phase, which are the required elements for the positive control in a QT trial (Fig. 2). These data confirm the assay sensitivity of this trial to detect any QT prolongation.

Table 2 Difference in QTcI from baseline and from placebo between 1.5 and 3 h post-dose

Treatment	n	Adjusted mean (SE) Δ QTcI (ms)	Mean (SE) [90 % CI] ΔΔ QTcI (ms)
Placebo	40	−4.6 (1.1)	
Dabigatran etexilate (150 mg)	40	−4.9 (1.1)	−0.2 (1.0) [−1.9, 1.4]
Dabigatran etexilate (600 mg)	40	−5.0 (1.1)	−0.4 (1.0) [−2.0, 1.3]
Placebo	40	−4.8 (1.0)	
Moxifloxacin (400 mg)	40	9.4 (1.0)	14.2 (1.2) [12.3, 16.2]

QTcI individually heart-rate–corrected QT interval, *SE* standard error, Δ change from baseline, ΔΔ placebo-corrected change from baseline

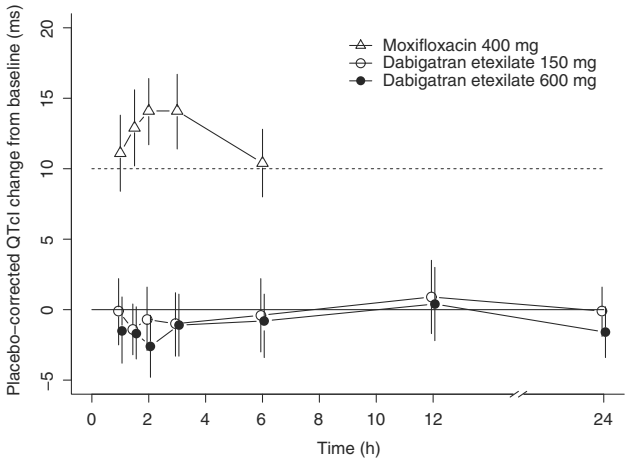

Fig. 2 Mean (±90 % confidence interval) placebo-corrected change from baseline of QTcI over time after dosing with dabigatran etexilate 150 mg, 600 mg and moxifloxacin 400 mg. *QTcI* individually heart-rate-corrected QT interval. *Dotted line* is the 10 ms non-inferiority margin

3.3 Other Parameters of Interest

3.3.1 Heart Rate, Uncorrected QT Intervals and Additional Heart-Rate–Corrected QT Intervals

RR-interval changes were minimal and the resulting heart rate change was less than 1 bpm. The various absolute QT(c) endpoints and CfBs did not differ by more than 1 ms for QTcN and QTcF from OTcI, slightly more for uncorrected QT and QTcB, and none of these parameters was prolonged with either dabigatran etexilate dose.

Although no systematic changes of heart rate were present in this study, heart rate correction formulae also adjust for random heart rate variability. The standard errors (and hence the widths of the CIs of the estimates) of the other heart-rate–corrected QTc intervals were higher than QTcI by up to 40 % (Table 3), similar to other TQT studies

Table 3 Comparison of placebo-corrected changes from baseline (ΔΔ) of QTcl, QT and heart rate over time in healthy subjects treated with dabigatran etexilate 150 mg, dabigatran etexilate 600 mg and moxifloxacin 400 mg

Time	ΔΔQTcI (ms)	ΔΔQT (ms)	ΔΔHR (bpm)
Dabigatran etexilate 150 mg (n = 40)			
1:00	−0.1 (−2.5 to 2.2)	−0.7 (−4.0 to −2.6)	0.7 (−0.5 to 1.8)
1:30	−1.4 (−3.2 to 0.4)	−0.6 (−3.3 to 2.1)	−0.3 (−1.4 to 0.8)
2:00	−0.7 (−2.9 to 1.6)	−0.2 (−2.9 to 2.6)	−0.3 (−1.5 to 0.8)
3:00	−1.1 (−3.3 to 1.2)	−1.9 (−4.9 to 1.0)	0.6 (−0.8 to 0.2)
6:00	−0.4 (−3.0 to 2.2)	−0.5 (−3.8 to 2.7)	0.1 (−1.4 to 1.2)
12:00	0.9 (−1.7 to 3.5)	1.3 (−1.8 to 4.5)	−0.4 (−1.7 to 0.9)
24:00	−0.1 (−1.9 to 1.7)	−0.2 (−2.8 to 2.5)	−0.1 (−1.1 to 1.0)
Dabigatran etexilate 600 mg (n = 40)			
1:00	−1.5 (−3.8 to 0.9)	−1.8 (−5.2 to 1.5)	0.5 (−0.6 to 1.6)
1:30	−1.7 (−3.5 to 0.2)	−0.6 (−3.3 to 2.1)	−0.3 (−1.5 to 0.8)
2:00	−2.6 (−4.8 to −0.4)	−0.9 (−3.7 to 1.8)	−1.1 (−2.2 to 0.1)
3:00	−1.1 (−3.3 to 1.1)	−2.9 (−5.8 to 0.1)	1.5 (−0.1 to 2.9)
6:00	−0.8 (−3.4 to 1.8)	−1.1 (−4.3 to 2.2)	0.6 (−0.7 to 1.9)
12:00	0.4 (−2.2 to 3.0)	1.0 (−2.1 to 4.2)	−0.2 (−1.5 to 1.1)
24:00	−1.6 (−3.4 to 0.2)	−3.1 (5.7 to 0.5)	1.1 (0.0 to 2.2)
Moxifloxacin 400 mg (n = 40)			
1:00	11.1 (8.4 to 13.8)	8.3 (4.7 to 11.9)	2.4 (0.9 to 3.8)
1:30	12.8 (10.2 to 15.6)	11.9 (8.3 to 15.5)	1.3 (0.1 to 2.5)
2:00	14.1 (11.7 to 16.5)	13.6 (10.4 to 16.9)	0.4 (−1.0 to 1.7)
3:00	14.1 (11.4 to 16.7)	10.3 (6.9 to 13.8)	2.7 (1.1 to 4.4)
6:00	10.4 (8.0 to 12.8)	9.2 (6.1 to 12.2)	1.5 (0.1 to 2.8)

Placebo-corrected changes from baseline are expressed as mean (90 % CI)

bpm beats per minute, *HR* heart rate, *QTcI* individually heart-rate–corrected QT interval

Table 4 Estimated maximum values for the placebo-corrected change from baseline (ΔΔ) of the QTcI and heart rate, as predicted by the exposure-response relationship of dabigatran etexilate, based on the concentration of free non-conjugated dabigatran and total (free and conjugated) dabigatran at the geometric mean of C_{max}

Analyte	Dose (mg)	gMean of C_{max} (ng/mL)	Exposure-response analysis for placebo-corrected CfB of QTcI			Exposure-response analysis for placebo-corrected CfB of HR		
			PK-ΔΔQTcI intercept (ms)	PK-ΔΔQTcI slope (ms/[ng/mL])	Predicted value of ΔΔQTcI at C_{max} (90 % CI) (ms)	PK-ΔΔHR intercept (bpm)	PK-ΔΔHR slope (bpm/[ng/mL])	Predicted value of ΔΔHR at C_{max} (90 % CI) (bpm)
Free non-conjugated dabigatran	150	71.4	0.34	0.0006	0.4 (−0.9 to 1.7)	0.26	0.0005	0.3 (−0.4 to 1.0)
	600	281			0.5 (−1.5 to 2.6)			0.4 (−0.9 to 1.7)
Total dabigatran (free and conjugated)	150	87.8	0.34	0.0006	0.4 (−0.9 to 1.7)	0.25	0.0003	0.3 (−0.4 to 1.0)
	600	383			0.6 (−1.3 to 2.5)			0.4 (−0.9 to 1.7)

bpm beats/min, *CfB* change from baseline, C_{max} maximum plasma concentration, *gMean* geometric mean, *HR* heart rate, *PK* pharmacokinetic, *QTcI* heart-rate–corrected QT interval

[33–35]. This strongly supports the use of QTcI as the primary correction method in this study.

3.3.2 ECG Safety Evaluation and Vital Signs

There were no notable changes in any of the subjects for heart rate or PR/QRS intervals. The overall quality of the ECG recordings was very good because there were no ECGs with findings impacting interval measurement.

Any findings relating to ECG or vital signs that deviated from normal were deemed reflective of the normal variations occurring in healthy subjects.

3.4 Pharmacokinetic Results

3.4.1 Dabigatran Plasma Concentration-Time Profiles

The plasma concentrations of total (free and conjugated) dabigatran rapidly increased following administration of dabigatran etexilate, with C_{max} at a median of 2–3 hours (Table 5). Mean C_{max} with dabigatran etexilate 600 mg was approximately fourfold higher than that achieved with dabigatran etexilate 150 mg (Table 5). Dabigatran etexilate and its intermediates (BIBR1087 and BIBR951) were only detectable between 0.5 and 3 h post-dosing and then only in very low concentrations.

3.5 Safety and Tolerability

Single oral doses of dabigatran etexilate 150 mg and 600 mg were well tolerated in this study. Global tolerability was reported as ‘good’ for all subjects and with all treatments, except for one subject who responded ‘not satisfactory’ after receiving moxifloxacin. A total of 21 subjects experienced at least one adverse event. All adverse events were of mild intensity and all subjects fully recovered. Five subjects reported adverse events during screening: headache (n = 3), back pain, allergic reaction (n = 1 each). During the three washout periods, adverse events were reported on ten occasions: herpes labialis (n = 3), headache (n = 2), flatulence, puncture-site pain, influenza-like symptoms, hayfever, diarrhoea (n = 1 each). Within the treatment period, adverse events were reported in three subjects (7.5 %) receiving dabigatran etexilate 150 mg (headache, heartburn, puncture-site haematoma) and four (10 %) receiving dabigatran etexilate 600 mg [puncture-site haematoma, hypermenorrhea, application-site allergy (i.e. electrode contact site), heartburn and headache]. One subject (2.5 %) reported ‘feeling dazed’ with moxifloxacin; dizziness and thoracic pain was recorded for one subject (2.5 %) receiving placebo. All bleeding events and the moxifloxacin-related adverse events were deemed to be drug related. Seven female subjects belatedly reported

Table 5 Dabigatran pharmacokinetics after single doses of dabigatran etexilate 150 mg and 600 mg

Parameter	Non-compartmental parameters of free non-conjugated dabigatran				Non-compartmental parameters of total dabigatran (free and conjugated)			
	Dabigatran etexilate 150 mg (n = 40)		Dabigatran etexilate 600 mg (n = 40)		Dabigatran etexilate 150 mg (n = 40)		Dabigatran etexilate 600 mg (n = 40)	
	gMean	gCV (%)	gMean	gCV (%)	gMean	gCV (%)	gMean	gCV (%)
AUC_{∞} (ng·h/mL)	540	74.3	2,230	43.5	703	71.5	3,070	42.1
C_{max} (ng/mL)	71.4	80.8	281	38.5	87.8	76.8	383	38.1
t_{max} (h)[a]	2.03	0.983–3.15	3.00	1.50–6.03	2.03	1.48–3.15	3.00	1.50–6.03

AUC$_{\infty}$ area under the plasma concentration-time curve from time zero to infinity, *C*$_{max}$ maximum observed plasma concentration, *gCV* geometric coefficient of variation, *gMean* geometric mean, *t*$_{max}$ time to reach C_{max}

[a] For t_{max}, the median and range (min to max) are given

increased menstrual flow; no correlation with dabigatran etexilate treatment was apparent. There were no deaths and no serious or significant adverse events reported.

4 Discussion

The aim of this study was to investigate whether therapeutic and supratherapeutic doses of dabigatran etexilate prolong the QT interval. Dabigatran etexilate 150 mg once daily is the lower of two doses available for primary VTE prevention following elective hip and knee replacement surgery [9, 10]. Dabigatran etexilate 150 mg twice daily is a dose approved for the prevention of stroke and systemic embolism in patients with non-valvular AF [7, 13–15, 36]. Based on previous PK studies [36, 37], 600 mg once daily was adopted as the supratherapeutic dose. Additionally, a single rather than a multiple [5] supratherapeutic dose design was adopted, allowing a higher maximum plasma level of the drug without compromising safety. In a pilot study, this dose resulted in a two- to threefold increase in the main coagulation parameter (activated partial thromboplastin time) achieved at 2–4 h post-dose. Higher doses were deemed inappropriate because the bleeding risk increases dose dependently [5, 37].

The PK results confirmed that the C_{max} after administering dabigatran etexilate 600 mg was approximately fourfold higher than that achieved with the 150-mg dose. This C_{max} is also 2.6 or 4 times higher than the steady-state concentration in patients receiving dabigatran etexilate 150 mg twice daily (146 ng/mL) or once daily (99.2 ng/mL), respectively [36]. Therefore, it is unlikely that the C_{max} in clinical use would usually exceed that of the supratherapeutic dose tested. Dabigatran etexilate has been administered to healthy volunteers at single doses up to 400 mg and multiple doses up to 400 mg three times daily for 6 days. The pharmacokinetic profile of a single dose of dabigatran etexilate predicted the steady-state pharmacokinetic profile of dabigatran; indeed, no time-dependent changes were observed in the pharmacokinetic profile of dabigatran after multiple dosing, despite accumulation seen with the three-times-daily regimen [38].

Although using single rather than multiple dosing might be considered a limitation in the design of thorough QT studies, a single-dose approach using a four-period crossover has been employed to test QT prolongation with other medications such as rivaroxaban, a direct factor Xa inhibitor [24], and eltrombopag, a thrombopoietin receptor agonist [25]. The rivaroxaban QT study [24] also employed the positive control moxifloxacin 400 mg and a placebo. While our study used a fourfold supratherapeutic dose of dabigatran etexilate, the rivaroxaban study used a threefold supratherapeutic dose [24]. Whereas the population in our study ranged in age from 24 to 53 years, the patients in the rivaroxaban trial were at least 50 years old [24]. Although most patients undergoing orthopaedic surgery or who have AF tend to be over 60 years of age, dabigatran etexilate is also being assessed for VTE treatment and these patients are likely to cover a wider age range [9, 10]. Therefore, this current safety study is relevant for patients who could potentially receive dabigatran etexilate in the future.

The control, moxifloxacin, was administered as commercially available capsules, with ECG recorded up to 6 h post-dose (rather than 24 h for dabigatran) and no pharmacokinetic sampling. Thus, treatment was double-blind for the two doses of dabigatran etexilate and placebo and open-label for moxifloxacin. Open-label assessment of moxifloxacin effects is a possible limitation of the study. Nonetheless, ECG intervals were measured in a fully blinded fashion at a central laboratory. The laboratory was audited to ensure that their blinding process for ECG evaluation was carried out correctly.

The primary formula used to correct the QT interval for heart rate was different than in other QT studies [24, 25, 39]. A study of the direct thrombin inhibitor AZD0837 in patients with atrial flutter used the Fridericia (QTcF)

formula [40]. Although both Fridericia and Bazett (QTcB) correction formulas are widely used, their accuracy and use have been criticized [41]. Thus, a formula using subject-specific baseline data for calculating the QT interval (QTcI) was primarily employed, similar to that used for the rivaroxaban QT study [24]. A recent white paper on QT interval correction in the presence of drug-induced heart rate changes has been published since we conducted our study [42]. Although we could have used an alternative method of heart rate correction as the primary formula, we have shown in our evaluation of different methods that this would have had very limited impact on the study results.

The primary endpoint of our study demonstrated non-inferiority for both doses of dabigatran etexilate (150 mg and 600 mg) compared with placebo. The upper limit of the 95 % CI was approximately 1.5 ms, which was significantly below the usual 10-ms margin for non-inferiority. Both doses of dabigatran etexilate were also non-inferior to placebo for the secondary endpoints. The upper limit of 95 % CI was below 4 ms, which was clearly lower than the 10-ms margin for non-inferiority. Furthermore, and as stated in the ICH E14 Guideline, drugs that prolong the mean QT or QTcl by around 5 ms or less do not appear to cause *torsade de pointes* [17]. Results from our study show that treatment with dabigatran etexilate does not prolong the QT interval by more than 5 ms, hence is not expected to treat serious cardiac pro-arrhythmias; this can therefore be termed a negative thorough QT study.

For the positive control moxifloxacin, the mean CfB of QTcI between 1.5 and 3 h post-dose was 9.4 ms, and 14.2 ms when compared with placebo. For all treatments and time intervals, changes in heart rate were nominal and within the range of ± 2.0 bpm. These findings are indicative of the robustness of the QT analyses performed in this study. The adverse events observed are consistent with those previously reported in trials examining the tolerability and safety of dabigatran etexilate at therapeutic or fourfold supratherapeutic doses [5]. No adverse event led to premature study discontinuation.

5 Conclusion

This study demonstrates that therapeutic (150 mg) and supratherapeutic (600 mg) doses of dabigatran etexilate are not associated with QT prolongation or arrhythmogenic effects. The risk of potential events related to QT prolongation or cardiac repolarization effects of dabigatran etexilate is therefore considered to be very low.

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